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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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IVOR R ELRIFI
MINTZ LEVIN COHN FERRIS
GLOVSKY & POPEO
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	24

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/331,980	CHAGNAUD ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-20* is/are pending in the application.

4a) Of the above claim(s) *7-10, 12-13 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,11 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/20/02 has been entered.

2. Claims 1-5, and 7-20 are pending.

3. Newly submitted claims 15-20 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 15-20 are drawn to a method of treating the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates by administering antibody that recognizes and binds specifically to a specific nitrosylated protein, classified in Class 424, subclass 141.1. A prior art search also requires a literature search. It is a burden for the examiner to search more than one invention. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 7-10, 12-13 and 15-20 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims 1-5, 11 and 14 drawn to a purified antibody that binds to specifically to a nitrosylated protein are being acted upon in this Office Action.

5. The substituted specification filed 10/21/02 has been entered.

6. The request to amend the specification (pages 1-11) of the amendment filed 11/20/03 has not been entered and will not be entered because the specified entries on pages and lines as to where the replacement be entered in the specification are no longer match with the substituted specification filed 10/21/02.

7. The drawings, filed 3/4/02, are not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. Appropriate action is required. It is noted that Applicants will provide formal figures upon receipt of a Notice of Allowance.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5, 11 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a purified antibody that binds specifically to NO-Cys-glutaraldehyde conjugated to a carrier protein such as BSA for detection assay, **does not** reasonably provide enablement for (1) *any* purified antibody that recognizes and binds specifically to any nitrosylated protein such that said purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in any subject; (2) the purified antibody that recognizes and binds specifically to any nitrosylated albumin such that said purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in any subject wherein the nitrosylated protein is a transporter of NO; (3) the purified antibody that recognizes and binds specifically to any nitrosylated albumin such that said purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in any subject; (4) the purified antibody that recognizes and binds specifically to any nitrosylated albumin such that said purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in any subject wherein the nitrosylated protein is a transporter of NO wherein the antibody is any polyclonal antibody or any monoclonal antibody; (5) any pharmaceutical composition comprising (a) any purified antibody that recognizes and binds specifically to any nitrosylated protein; and (b) a pharmaceutically acceptable excipient; wherein said purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in a subject for treating any disease, and (6) a kit for in vitro detection of any nitrosylated proteins in biological specimen, comprising: (a) any purified antibody that recognizes and binds specifically to any nitrosylated protein; and (b) reagents to produce a medium favorable for an immunological reaction between said purified antibody and any nitrosylated proteins that may be present in a biological specimen. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two polyclonal antibodies that bind specifically to nitrosylated cysteine-glutaraldehyde conjugated to BSA (NO-Tyr-BSA) or NO-Cys-BSA) for in vitro and in vivo detection assays (page 33). The specification further discloses monoclonal antibody that binds specifically to NO-Cys-G protein conjugate for in vitro detection of certain NO binding sites such as cysteine in parasites (page 38).

The specification does not teach how to make any antibody that binds to any nitrosylated protein, much less using any undisclosed antibody for neutralizing the deleterious effects of "inadequate production of nitric oxide" or its conjugates in a subject. There is insufficient guidance as to the binding specificity of any undisclosed antibody that binds to any nitrosylated protein. Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the indefinite number of nitrosylated protein and without the specific amino acid sequence to which the undisclosed antibody binds, it is unpredictable which undisclosed antibody generated from any nitrosylated protein would binds specifically to NO-Cys-glutaraldehyde conjugated to BSA, in turn, would be useful for neutralizing the deleterious effects of excessive production of nitric oxide such as autoimmune arthritis, EAE in a subject or neutralizing the deleterious effects of "inadequate production of nitric oxide".

Even if the antibody is limited to the specific antibodies mentioned above, there is no in vivo working example demonstrating that the antibodies mentioned above are effective for neutralizing the deleterious effects of "inadequate production of nitric oxide" or its conjugates in any subject. It is known that excessive nitric oxide production by activated macrophage may be one of the causes for the deleterious effects in inflammatory rheumatoid arthritis. However, it is not known that "inadequate production of nitric oxide" is the cause of any inflammatory disease and antibody that binds to *any* "nitrosylated protein" is effective for treating said inflammatory disease. The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering any antibodies that neutralizes the deleterious effects of inadequate production of nitric oxide or its conjugates. The specification does not teach how to extrapolate data obtained from in vitro detection assays to the development of effective in vivo human therapeutic compositions, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the antibodies exemplified in the specification for treating any diseases encompassed by the claims.

As to claim 14, since the binding specificity of any antibody is not enabled, it follows that a kit for in vitro detection of any nitrosylated proteins in biological specimen is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

10. Claims 1-5, 11 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* purified antibody that recognizes and binds specifically to any nitrosylated protein such that said purified

antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in any subject; (2) the purified antibody that recognizes and binds specifically to any nitrosylated albumin such that said purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in any subject wherein the nitrosylated protein is a transporter of NO; (3) the purified antibody that recognizes and binds specifically to any nitrosylated albumin such that said purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in any subject; (4) the purified antibody that recognizes and binds specifically to any nitrosylated albumin such that said purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in any subject wherein the nitrosylated protein is a transporter of NO wherein the antibody is any polyclonal antibody or any monoclonal antibody; (5) any pharmaceutical composition comprising (a) any purified antibody that recognizes and binds specifically to any nitrosylated protein; and (b) a pharmaceutically acceptable excipient; wherein said purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in a subject for treating any disease, and (6) a kit for in vitro detection of any nitrosylated proteins in biological specimen, comprising: (a) any purified antibody that recognizes and binds specifically to any nitrosylated protein; and (b) reagents to produce a medium favorable for an immunological reaction between said purified antibody and any nitrosylated proteins that may be present in a biological specimen.

The specification discloses only two polyclonal antibodies that bind specifically to nitrosylated cysteine-glutaraldehyde conjugated to BSA (NO-Tyr-BSA) or NO-Cys-BSA) for in vitro and in vivo detection assays (page 33). The specification further discloses monoclonal antibody that binds specifically to NO-Cys-G protein conjugate for in vitro detection of certain NO binding sites such as cysteine in parasites (page 38).

With the exception of the specific antibodies for detection assay, there is insufficient written description about the binding specificity of any purified antibody that binds to *any* nitrosylated protein for neutralizing the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in any subject. Further, the specification discloses only three antibodies that bind specifically to NO-Tyr-BSA, NO-Cys-BSA and NO-Cys-G protein conjugate. Given the lack of a written description of *any* additional representative species of antibodies in a pharmaceutical composition for treating any inflammatory disease as a consequence of excessive or inadequate production of nitric oxide or its conjugate, one of skill in

the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Since the binding specificity of any antibody is not adequately described, it follows that a kit for in vitro detection of any nitrosylated proteins in biological specimen is not adequately described.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. Claims 1-5 and 11 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates in a subject" in Claims 1 and 11 represents a departure from the specification and the claims as originally filed. The specification discloses on page 33 that polyclonal antibody neutralizes the NO-BSA trypanostatic effect in culture and not in a subject. Further, the phrase "inadequate production of nitric oxide or its conjugates" has no support in the specification as filed. Applicant has not pointed out the support for said phrase.

12. The filing date of the instant claims 1-5, 11 and 14 is deemed to be the filing date of PCT/FR97/02412 filed 12/23/1997 because a translation of said priority document has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. Further, the foreign document is in French and the Examiner cannot determine the scope and content said foreign document.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

14. Claims 1-4 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Mnaimneh *et al* (J Immunology 158(1): 308-14, Jan 1, 1997; PTO 892).

Mnaimneh *et al* teach an isolated antibody such as polyclonal Abs that binds specifically to nitrosylated protein such as NO-ac-Cys-BSA (See abstract, Materials and Methods, in particular). The reference Anti-NO-ac-Cys antibody neutralizes the antimicrobial effect of activated macrophages on the extracellular parasite, T musculi or Calmette-Guerin bacillus-activated macrophages. The reference nitrosylated albumin inherently is a transporter of NO. Given that the reference antibody can neutralizes the deleterious effects of excessive production of nitric oxide produced by macrophage in vitro, the reference antibody inherently would also neutralizes the deleterious effects of excessive production of nitric oxide produced by macrophage in vivo. Mnaimneh et al teach that a pharmaceutical acceptable excipient such as PBS 9See page 309, column 1, Antiserum preparation, in particular). Mnaimneh *et al* teach that antibody against nitrosoproteins could also block the effects of NO compounds in vivo and protect specifically against some of their (NO) harmful properties (See page 313, column 1, in particular). Thus, the reference teachings anticipate the claimed invention.

15. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Boullerne *et al.* (of record, J. of Neuroimmunology 60: 117-124, 1995; PTO 892).

Boullerne *et al* teach a purified antibody that recognizes and binds specifically to a nitrosylated protein such as nitrosylated bovine serum albumin. The reference autoantibody isolated from sera of Multiple sclerosis (MS) is polyclonal (See page 123, column 1, first paragraph, in particular). Boullerne et al further teach that the reference antibody can be purified using nitrosylated carrier protein (nitrosylated bovine serum albumin) or a nitrosylated amino acid (cysteine) coupled to a carrier (bovine serum albumin) by a coupling agent which is glutaraldehyde (g) (See NO-Cys-g-BSA in **Materials and Methods**, pp. 118-119, in particular). Antibody to the nitrosylated bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA) to detect nitrosylated protein in the sera of patients with multiple sclerosis (See page 119, column 1, in particular). Boullerne *et al* further teach that NO production may be involved in autoimmune diseases including IDDM, SLE, autoimmune neuropathy of Chagas' disease caused by trypanosoma cruzi and the use of conjugated haptens (nitrosylated cysteine cross-linked to BSA) is very helpful in defining the specific antibody responses (See page 123, column 1, last paragraph, in particular). Claim 2 is included in this rejection because Nitrosylated

protein inherently is a transporter of nitric oxide. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 11/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Boullerne does not provide any teaching directed to a purified antibody that recognizes and binds specifically to a nitrosylated protein such that the purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates.

However, a product is a product irrespective of its intended uses. Further, the specificity of the claimed antibody appears to the same as that of the prior art. Boullerne *et al* teach a purified antibody that recognizes and binds specifically to a nitrosylated protein such as nitrosylated bovine serum albumin. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mnaimneh *et al* (J Immunology 158(1): 308-14, Jan 1, 1997; PTO 892) in view of U.S. Pat No. 6,090,382 (July 2000, PTO 892) and Campbell *et al* (of record, Monoclonal antibody technology , Elsevier Science Publishers, 1984) or Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149).

The teachings of Mnaimneh *et al* have been discussed supra.

The claimed invention in claim 5 differs from the teachings of the reference only that the antibody is a monoclonal antibody.

The '382 patent teaches a pharmaceutical composition comprising an antibody that binds to human TNFα and a pharmaceutical acceptable carrier or excipient such as sterile saline (See column 20 lines 57, bridging column 21, line 1-52, in particular).

Campbell *et al* teach that "[i] it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (See page 29, section "Basic research", in particular).

Harlow *et al* teach a method of producing monoclonal antibody (See page 139-149, in particular). Harlow *et al* further teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody as taught by Campbell *et al* or Harlow *et al* with the nitrosylated protein as taught by Mnaimneh *et al* for a pharmaceutical composition comprising a monoclonal antibody that binds specifically to said nitrosylated protein and a pharmaceutical excipient as taught by the '382 patent, Campbell *et al*, Harlow *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody fragment because Harlow *et al* teach the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Campbell *et al* teach that "[i] it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (See page 29, section

"Basic research", in particular). Mnaimneh *et al* teach that antibody against nitrosoproteins could also block the effects of NO compounds in vivo and protect specifically against some of their (NO) harmful properties (See page 313, column 1, in particular).

19. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mnaimneh *et al* (J Immunology 158(1): 308-14, Jan 1, 1997; PTO 892) in view of U.S. Pat No. 6,090,382 (July 2000, PTO 892) and Campbell *et al* (of record, Monoclonal antibody technology , Elsevier Science Publishers, 1984) or Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149) as applied to claims 1 and 5 and further in view of U.S. Pat No. 5,858,682 (of record, Jan 1999, PTO 892; see entire document).

The combined teachings of Mnaimneh *et al,* the 382 patent, Campbell *et al* and Harlow et al have been discussed supra.

The claimed invention in claim 14 differs from the teachings of the references only that a kit for in vitro detection of nitrosylated proteins in biological specimen comprising a purified antibody that recognizes and binds specifically to a nitrosylated protein and reagents to produce a medium favorable for an immunological reaction between said purified antibody and any nitrosylated proteins that may be present in a biological specimen.

The '682 patent teaches a kit comprising antibody for diagnostic (See column 3, line 40; column 6, line 17; column 8, line 36, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody in a kit taught by '682 with the polyclonal antibody that binds nitrosylated protein taught by as taught Mnaimneh *et al* or the monoclonal antibody that binds specifically to the nitrosylated protein as taught by Mnaimneh *et al* and Campbell or Harlow et al for the detection of nitrosylated protein immune complex in any biological specimen as taught by Mnaimneh *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One would have been motivated, with a reasonable expectation of success, to place the antibody in a kit for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '682 (See column 8, line 36-57, in particular).

20. Claims 1, 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boullerne *et al.* (of record, J. of Neuroimmunology 60: 117-124, 1995; PTO 892) or Stamler *et al*, (of record, Proc. Natl. Acad. Sci USA 89: 444-448, 1992; PTO 892) each in view of Mnaimneh *et al* (J Immunology 158(1): 308-14, Jan 1, 1997; PTO 892), U.S. Pat No. 6,090,382 (July 2000, PTO 892) and Campbell *et al* (of record, Monoclonal antibody technology , Elsevier Science Publishers, 1984) or Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149).

Boullerne *et al* teach nitrosylated carrier protein such as nitrosylated bovine serum albumin or a nitrosylated amino acid (cysteine) coupled to a carrier (bovine serum albumin) by a coupling agent which is glutaraldehyde (g) (See NO-Cys-g-BSA (See Materials and Methods, pp. 118-119, in particular). Boullerne *et al* teach antibody to the nitrosylated bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA) to detect nitrosylated protein in the sera of patients with multiple sclerosis (See page 119, column 1, in particular). Boullerne *et al* further teach that NO production may be involved in autoimmune diseases such as IDDM, SLE, autoimmune neuropathy of Chagas' disease caused by trypanosoma cruzi and the use of conjugated haptens (nitrosylated cysteine cross-linked to BSA) is very helpful in defining the specific antibody responses (See page 123, column 1, last paragraph, in particular).

Stamler *et al* teach a method of synthesizing S-Nitroso proteins such as nitroso BSA, t-PA, Cathepsin B and human plasma. Stamler *et al* further teach nitric oxide (NO) has a half-life in the order of 0.1 second *in vivo* and nitrosylation of NO increases the half-life of these NO molecules to about 24 hour (See page 444, column 1, 1st paragraph; page 445, column 2 Results; page 446, column 1, last paragraph, in particular).

The claimed invention in claim 5 differs from the teachings of the references that the antibody is a monoclonal antibody.

The claimed invention in claim 11 differs from the teachings of the references only a pharmaceutical composition comprising (a) a purified antibody that recognizes and binds specifically to a nitrosylated protein and (b) a pharmaceutically acceptable vehicle wherein the purified antibody neutralizes the deleterious effects of excessive production of nitric oxide in a subject.

Mnaimneh *et al* teach an isolated antibody such as polyclonal Abs that binds specifically to nitrosylated protein such as NO-ac-Cys-BSA (See abstract, Materials and Methods, in particular). The reference Anti-NO-ac-Cys antibody neutralizes the antimicrobial effect of

activated macrophages on the extracellular parasite, T musculi or Calmette-Guèrin bacillus-activated macrophages. The reference nitrosylated albumin inherently is a transporter of NO. Given that the reference antibody can neutralizes the deleterious effects of excessive production of nitric oxide produced by macrophage in vitro, the reference antibody inherently would also neutralizes the deleterious effects of excessive production of nitric oxide produced by macrophage in vivo. Mnaimneh et al teach that a pharmaceutical acceptable excipient such as PBS 9See page 309, column 1, Antiserum preparation, in particular). Mnaimneh *et al* teach that antibody against nitrosoproteins could also block the effects of NO compounds in vivo and protect specifically against some of their (NO) harmful properties (See page 313, column 1, in particular).

The '382 patent teaches a pharmaceutical composition comprising an antibody that binds to human TNFα and a pharmaceutical acceptable carrier or excipient such as sterile saline (See column 20 lines 57, bridging column 21, line 1-52, in particular).

Campbell *et al* teach that "[i] it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (See page 29, section "Basic research", in particular).

Harlow *et al* teach a method of producing monoclonal antibody (See page 139-149, in particular). Harlow *et al* further teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody as taught by Campbell *et al* or Harlow *et al* with the nitrosylated protein as taught by Boullerne *et al*, Stamler *et al* or Mnaimneh for a pharmaceutical composition comprising a monoclonal antibody that binds specifically to the nitrosylated protein and a pharmaceutical excipient as taught by the '382 patent and Mnaimneh et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody fragment because Harlow *et al* teach the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Campbell *et al* teach that "[i] it is customary now for any

group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (See page 29, section "Basic research", in particular). Mnaimneh *et al* teach that antibody against nitrosoproteins could also block the effects of NO compounds in vivo and protect specifically against some of their (NO) harmful properties (See page 313, column 1, in particular). Boullerne *et al* teach antibody to the nitrosylated bovine serum albumin can be use in Enzyme-linked immunosorbent Assay (ELISA) to detect nitrosylated protein in the sera of patients with multiple sclerosis (See page 119, column 1, in particular); NO production may be involved in autoimmune diseases including IDDM, SLE, autoimmune neuropathy of Chagas' disease caused by trypanosoma cruzi and the use of conjugated haptens (nitrosylated cysteine cross-linked to BSA) is very helpful in defining the specific antibody responses (See page 123, column 1, last paragraph, in particular). Stamler *et al* teach nitric oxide (NO) has a half-life in the order of 0.1 second *in vivo* and nitrosylation of NO increases the half-life of these NO molecules to about 24 hour (See page 444, column 1, 1st paragraph; page 445, column 2 Results; page 446, column 1, last paragraph, in particular).

Applicants' arguments filed 11/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Boullerne does not provide any teaching directed to a purified antibody that recognizes and binds specifically to a nitrosylated protein such that the purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates.

However, a product is a product irrespective of its intended uses. Further, the specificity of the claimed antibody appears to the same as that of the prior art. Boullerne *et al* teach a purified antibody that recognizes and binds specifically to a nitrosylated protein such as nitrosylated bovine serum albumin. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Further, Mnaimneh *et al* teach that antibody against nitrosoproteins could also block the effects of NO compounds in vivo and protect specifically against some of their (NO) harmful properties (See page 313, column 1, in particular).

21. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boullerne *et al.* (of record, J. of Neuroimmunology 60: 117-124, 1995; PTO 892) or Stamler *et al*, (of record, Proc. Natl. Acad. Sci USA 89: 444-448, 1992; PTO 892) each in view of Mnaimneh *et al* (J Immunology 158(1): 308-14, Jan 1, 1997; PTO 892), U.S. Pat No. 6,090,382 (or record, July 2000, PTO 892) and Campbell *et al* (of record, Monoclonal antibody technology , Elsevier Science Publishers, 1984) or Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149) as applied to claims 1, 5 and 11 mentioned above, and further in view of U.S. Pat No. 5,858,682 (of record, Jan 1999, PTO 892; see entire document).

The combined teachings of Boullerne *et al*, Stamler *et al*, Mnaimneh *et al*, the '382 patent, Campbell *et al* and Harlow *et al* have been discussed supra.

The claimed invention in claim 14 differs from the teachings of the references only that a kit for in vitro detection of nitrosylated proteins in biological specimen comprising a purified antibody that recognizes and binds specifically to a nitrosylated protein and reagents to produce a medium favorable for an immunological reaction between said purified antibody and any nitrosylated proteins that may be present in a biological specimen.

The '682 patent teaches a kit comprising antibody for diagnostic (See column 3, line 40; column 6, line 17; column 8, line 36, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody in a kit taught by '682 with the polyclonal antibody that binds nitrosylated protein taught by as taught by Boullerne *et al,* Stamler *et al,* or Mnaimneh *et al* or the monoclonal antibody by binds specifically to nitrosylated protein as taught by Boullerne *et al,* Stamler *et al* and Campbell *et al* or Harlow *et al* for the detection of nitrosylated protein immune complex in any biological specimen as taught by Boullerne *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One would have been motivated, with a reasonable expectation of success, to place the antibody in a kit for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '682 (See column 8, line 36-57, in particular).

Applicants' arguments filed 11/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Boullerne does not provide any teaching directed to a purified antibody that recognizes and binds specifically to a nitrosylated protein such that the purified antibody neutralizes the deleterious effects of excessive or inadequate production of nitric oxide or its conjugates.

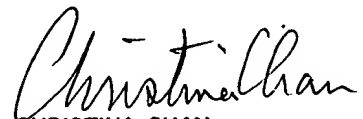
However, a product is a product irrespective of its intended uses. Further, the specificity of the claimed antibody appears to the same as that of the prior art. Boullerne *et al* teach a purified antibody that recognizes and binds specifically to a nitrosylated protein such as nitrosylated bovine serum albumin. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Further, Mnaimneh *et al* teach that antibody against nitrosoproteins could also block the effects of NO compounds in vivo and protect specifically against some of their (NO) harmful properties (See page 313, column 1, in particular).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

24. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
August 25, 2003



CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600